Comments of

American Composites Manufacturers Association

National Marine Manufacturers Association

Styrene Information and Research Center

Regarding

The National Toxicology Program's proposed revisions to the Report on Carcinogens review process

November 30, 2011

1. Introduction.

The American Composites Manufacturers Association,[1] the National Marine Manufacturers Association,[2] and the Styrene Information and Research Center[3] are pleased to provide these comments to the U.S. Department of Health and Human Services (HHS) National Toxicology Program (NTP) in response to the Oct. 31, 2011, Proposed Review Process for the *Report on Carcinogens* (*RoC*).[4]

The styrene industry submitted numerous comments to NTP, both when the *RoC* process was under review prior to initiating, and then during development of the 12th *RoC*. Our direct experience with NTP's assessment and listing of styrene in the 12th *RoC* has provided us with unique, in-depth, and valuable perspectives of potential issues associated with implementation of what was already a new process at that time. This direct and intensive experience puts us in a strong position to offer credible public comment on the merits of this additional attempt by NTP to modify its *RoC* process.

We agree with NTP that significant steps must be taken to improve the *RoC* process, but not as outlined in the current proposal. Unfortunately, this proposal moves in the wrong direction – toward administrative convenience for the staff and away from badly needed improvement in transparency, stakeholder participation, peer review, reliability and quality. The NTP proposal violates the Administration's March 2009 memorandum on scientific integrity by decreasing opportunities for public participation and reducing transparency in the preparation and review of the *RoC*.

We are further astonished that the NTP has apparently developed these proposed changes with complete disregard for the recent recommendations of the National Academy of Sciences (NAS) regarding the proper framework for hazard assessments such as the *Report on Carcinogens* and the repeated sharp criticisms of the scientific and procedural flaws in the current process by the scientific community and Congress. NTP's refusal to acknowledge any criticism of its process and respond appropriately is compounded by NTP's proposed process changes that reinstate outdated and inappropriate practices that were specifically rejected in the reformed process imposed on NTP by the White House Office of Management and Budget (OMB) and the HHS Secretary's Office for the 12th *RoC*. In short, not only does NTP fail to correct the serious flaws in the 12th *RoC* process, NTP proposes now to

[1] The American Composites Manufacturers Association (ACMA) is the national trade group for the composites industry. Our members include some 3,000 small and medium-sized companies, employing some 250,000 Americans, that use combinations of styrene polyester thermoset plastic resin, glass fiber and other materials to make underground gasoline storage tanks and pollution control equipment, wind turbine blades, modular tub/shower units and bathroom vanities, ballistic panels and armor for military vehicles, fiberglass recreational boats, automotive, truck and motorhome components, window lineal and ladder rail, bridge decks and concrete reinforcing bars, playground equipment, components for commercial and military aircraft, signs and building fascia, and thousands of other composites products, as well as the suppliers of raw material to this industry. Correspondence to ACMA should be directed to John Schweitzer, Senior Director of Government Affairs, 3033 Wilson Blvd., Suite 420, Arlington VA 22201.

[2] The National Marine Manufacturers Association (NMMA) is the nation's largest recreational marine industry association, representing more than 1,300 boat builders, engine manufacturers, and marine accessory manufacturers. NMMA members collectively produce more than 80 percent of all recreational marine products made in the United States. Recreational boating is a popular American pastime, with almost 75 million boaters nationwide and over 16.67 million boats in use. The recreational boating industry is a substantial contributor to the nation's economy with sales of recreational marine products and services of over $30.4 billion in 2010 alone. There are currently 1,125 boat manufacturing facilities in the United States. The vast majority of boat builders are small businesses. Correspondence to NMMA should be directed to Jeffrey Gabriel, Legislative Counsel, 444 N. Capitol Street, NW, Suite 645, Washington, DC 20001.

[3] The Styrene Information and Research Center (SIRC) was formed in 1987 as the principal focal point for public information and research on styrene. It is a non-profit organization consisting of voting member companies involved in the manufacturing or processing of styrene, and associate member companies that fabricate styrene-based products. Collectively, SIRC's membership represents approximately 95% of the North American styrene industry. SIRC serves as a liaison between industry, federal and state governments, and international agencies on health-related issues involving styrene. Correspondence to SIRC should be directed to Jack Snyder, Executive Director,1655 N. Fort Myer Drive, Suite 700, Arlington, VA 22209.

[4] 76 FR 67200.

make the process even less valid, much less scientifically robust, and the *RoC* far less useful as a product intended to advance public health.

The current proposed process is so fundamentally flawed that **NTP should withdraw these changes from consideration**. NTP's Board of Scientific Counselors (BSC) should insist that NTP do so. In its place, in collaboration with the BSC, NTP should substitute a deliberative, open dialogue with stakeholders, starting with a blank page to consider what process elements and flow are essential to ensure transparent, efficient and scientifically valid reviews of substances for listing in the *RoC*.

The obvious and significant flaws with NTP's assessments for the *RoC* have been forcefully and repeatedly brought to the attention of HHS and NTP by members of Congress. For example, in May 2011, 63 House Members wrote to HHS Secretary Kathleen Sebelius to express concerns about the poor scientific quality of the NTP styrene review, and another 50 House members wrote to the White House on November 9, 2011 to request an NAS review of NTP's styrene listing.

2. NTP's proposed process fails to implement essential and widely accepted principles of scientific review, and ignores NAS recommendations.

There are a number of accepted principles for scientific reviews conducted to support governmental hazard and risk assessments. Several of these principles have been the subject of White House directives and memos, including those by the Obama administration, and the significance of others was recently confirmed by the NAS. Still others were the subject of public comments to NTP during development of the 12th *RoC*.

In Table 1 of these comments, we list these accepted principles and explain how they were satisfied, or not, under the process employed by NTP for the 12th *RoC*, and how they would fare under the proposed new process. In summary the updated *RoC* process should:

- **Require standard protocols called for by the National Academy of Sciences:** The process employed for the 12th *RoC* had little of the standardization called for by the NAS in its recent commentary on federal hazard and risk assessment programs.[5] NTP's one recognized standard – for peer review – was in at least three cases disregarded by the staff. Instead of proposing standard protocols as called for by the NAS, NTP's proposal specifically seeks flexibility to treat each substance differently. Thus, the proposed process would move even further away from the standardization insisted upon by NAS.

- **Apply the Weight-Of-The-Evidence Analyses:** NTP did not use the recommended and widely accepted weight-of-the-evidence process for the 12th *RoC*. NTP's formal procedures for weighing evidence in the process of applying its listing criteria[6] are largely opaque and, judging from the results, largely biased. From an early stage of the review process, NTP brought forward for peer review only the limited positive data supporting the staff's position while ignoring or failing to address data that contradicted or failed to support that position. NTP's proposed process makes no effort to improve its listing criteria – which date to the 1970s, while the understanding of carcinogenicity and predicting cancer in humans has made

[5] Chapter 7 of the NAS *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde.* April, 2011. www.nap.edu/catalog.php?record_id=13142.
[6] NTP Listing Criteria: http://ntp.niehs.nih.gov/go/15209.

enormous progress in the past 30 years.[7] Worse still, the Concept Document to be prepared early in NTP's assessment is to contain "evidence for carcinogenicity" (emphasis added) as contrasted with the Background Document prepared for the 12th *RoC* that at least was represented by NTP staff as presenting all the data including negative data.[8]

- **Ensure Rigorous Peer Review:** NTP staff was able to control and compromise the independence of peer reviews during the 12th *RoC* process by 1) using a closed process for identification and selection of scientists for its Expert Panels; 2) failing to facilitate effective review of outside scientific comments by the governmental panels and the BSC; 3) presenting the BSC with highly constrained charge questions that effectively avoided the critical question of whether the data on a substance actually support a significant concern for cancer; 4) ignoring advisory panels when they voted not to list a substance; 5) providing responses to the scientific merits of external scientific comments only after the 12th *RoC* report was formally issued (and then in only the most meager and reluctant fashion); and 6) denying the BSC a formal "yes or no" vote on the application of the listing criteria to the substance and the staff's listing recommendation. Under NTP's newly proposed process, the staff would have even more control over the nature and extent of peer review, further diminishing its quality and effectiveness. For example, the staff would be allowed to skip final review by the BSC altogether and instead put together an ad hoc panel of their own choosing to peer review the staff's work.

- **Use Comments by Outside Scientists to Highlight Major Scientific Issues for Reviewers:** For the 12th *RoC*, NTP responded to outside scientific comment only well after this information could have an impact on the outcome of the assessment (only after the Report was formally issued). The two governmental panels, the BSC, and the Secretary all were denied meaningful opportunities to "reality check" the staff's position by comparing it to the positions of outside scientists. The proposed process makes no effort to improve the timeliness and value of outside input. Worse, opportunities for the public to provide information before preparation of the Concept Document, and in response to a draft of the Document, are removed from the process. NTP has even removed the requirement for it to respond to public comment at the end of the process, only requiring NTP to belatedly respond to whatever external peer review report it chooses to commission.

- **Avoid Conflicts of Interest:** Two members of NTP's Styrene Expert Panel for the 12th *RoC* arguably had intellectual conflicts of interest that may have contaminated the Panel's conclusion. NTP refused to acknowledge this as a potential problem and made no effort to manage the process to avoid contamination. The proposed process, with even less standardization of peer review, can only be more susceptible to conflict of interest problems.

[7] Starting with the issuance in 1983 of *Risk Assessment in the Federal Government: Managing the Process*, by the National Research Council.
[8] In the past, NTP has justified its approach by maintaining that the *RoC* represents only the first step in risk assessment, that is, hazard identification. This position, however, is incorrect, and we ask the NTP explicitly recognize this. It should be evident that the fundamental task of an *RoC* listing comprises a risk assessment warranting a weight of evidence evaluation. These tasks include: (1) distinguishing between known and reasonably anticipated carcinogens, with the obvious task of not listing carcinogens that fall outside those categories, (2) finding that the candidate substance is a human carcinogen, and (3) determining that the U.S. population is exposed to the substance amounts that reasonably warrant a health concern. While an *RoC* listing does not require NTP to prepare a mathematical description of carcinogenic potency, the absence of that specific element is not a basis for NTP to reject the routine use of weight of evidence analysis for each listing.

Overall, it is clear that NTP failed to adhere to these accepted best practices during its review for the 12th *RoC*, and further that the proposed new process would only make matters worse. NTP needs to withdraw the proposed process and start with a careful examination of these basic principles.

3. NTP has not usefully disclosed its view of how the *RoC* is broken or how its proposal will make the program better.

NTP's proposed revisions include no changes that would address significant flaws that became apparent during preparation of the 12th *RoC*. NTP's proposed revisions diminish the value of peer review, reduce opportunities for the public to provide useful scientific and policy input, isolate NTP from the responsibility to provide timely and productive responses to public comment and peer review, and decrease transparency.

The proposed new *RoC* process reverses several of the changes implemented for the 12th *RoC*, which were designed to increase transparency, attention to outside scientific input, and scientific validity (which desired improvements were nevertheless effectively frustrated and largely denied by NTP's management). These changes for the 12th *RoC* were implemented in consultation with the OMB to bring the *RoC* process into close alignment with the Peer Review Bulletin.[9] NTP has not disclosed how and when it proposes to similarly consult with OMB regarding its proposed revisions and how its changes comply with these executive branch requirements.

Since NTP has not disclosed in any meaningful detail its objectives for the revised process, it will be impossible for the public or the BSC to judge whether the proposed changes are in fact likely to satisfy the objectives.

4. Conclusion.

We call on NTP to withdraw the proposed new process. In its place, in collaboration with the BSC, the NTP should substitute a deliberative, open dialogue with stakeholders, specifically starting with a blank page to consider what process elements and flow are needed to ensure transparent, efficient and scientifically valid reviews of substances for listing in the *RoC*.

The NTP actions for developing public and BSC comment to the *RoC* process proposal signal a distinct failure of NTP to recognize the serious implications of the proposed changes to affected stakeholders, the public and the scientific community. We find it highly implausible that NTP is truly serious about establishing a credible new process in meaningful consultation with the public. If that were the case, then certainly it would allow more than a brief four-week time period for public response to its proposal followed by only a subsequent two-week interval between receipt of public comment and presentation of the revised process to the BSC for final advisory comment.

Attachment: Table 1.

[9] 70 FR 2640.

Principle of scientific review to support hazard assessment	NTP's performance during the 12th RoC	NTP's new proposed RoC process
Standardized guidelines for data identification, review and characterization The NAS "roadmap"[i] calls for the following steps as part of hazard assessment: ● Establish standard protocols for evidence identification. ● Develop a template for description of the search approach. ● Establish protocols for review of major types of studies, such as epidemiologic and bioassay. ● Expand and harmonize the approach for characterizing uncertainty and variability. ● Establish clear guidelines for study selection. To improve the use of science in regulatory policy, the Bipartisan Policy Center has advised that: Agencies and their scientific advisory committees should be explicit about the criteria they are using to determine which scientific papers to review and how those papers are being evaluated. Those criteria should be open for public comment either as part of the comment period on a proposed rule or, when possible, earlier in the rulemaking process.[ii]	NTP does not appear to have standard protocols for evidence identification. The only concrete constraint appears to be that data used must be publicly available and peer reviewed. However, in the case of styrene, NTP ignored the peer review requirements for its own novel reinterpretations of otherwise peer-reviewed analyses and conclusions (while using the requirement to restrict the introduction of new studies awaiting publication that countered NTP's conclusions). The NTP process allows the public to submit information to be considered in the nomination and delisting processes. However, NTP staff make the determination whether such information is relevant and should therefore be included in the documents NTP directly provides to peer reviewers. NTP is not obligated to offer any public response to its decisions on data to be included for evaluation until after the formal RoC listing is completed. NTP has no clear criteria for the review of major types of studies. It does not describe how it chooses between studies for inclusion in substance profiles. Its peer review process appears aimed at answering the question of whether the data selected and presented by NTP can be used to justify a determination rather than whether it is the right information or the correct determination. Other than a cursory discussion of limitations of the studies that it chooses to use to support a decision, NTP has no formal or standardized approach for considering uncertainty and strengths and weaknesses of individual studies in its assessments.	The proposed process moves even further away from the standardization insisted upon by NAS. Under the proposed process, NTP could manage the review of each substance entirely differently, leading to a mishmash of reviews entirely dependent on the opinions and varying procedural decisions of NTP staff. For example should the proposed revisions be adopted, stakeholders would have no certainty or say regarding what data will be collected and analyzed in the several critical stages of the review, including evaluation of carcinogenicity to determine if a nomination should be accepted; identification and weighing of studies to prepare the concept document; selection of the approach for development of the cancer evaluation component of the draft monograph; identification and weighing of studies to prepare a cancer evaluation for the monograph; selection of data for evaluation using the listing criteria; and preparation of the peer review report. The proposed peer review of the draft monograph includes consideration of a few of the critical issues including whether the scientific evidence is objectively presented and adequate for applying the listing criteria, and whether NTP staff have made a scientifically supportable determination regarding listing. However, this review comes too late in the process, after NTP has already made a significant commitment to the proposed listing recommendation. Further, NTP is free to ignore the opinions of the BSC or panel members, as it has in the past, and can manage the review to minimize or prevent meaningful consideration of outside scientific input.

Principle of scientific review to support hazard assessment	NTP's performance during the 12th RoC	NTP's new proposed RoC process
Weight-of-the-evidence assessment The recent NAS roadmap reconfirmed the importance of using weight-of-the-evidence (WoE) assessment in conducting hazard and risk evaluations. A WoE assessment characterizes the likelihood of a common thread tying together evidence from human, animal and metabolism studies, and proposes a biologically plausible line of reasoning why a potential hazard in humans is indicated.[iii] According to the NAS, hazard assessment (the explicit purpose of the RoC) answers the question, "Does the agent cause the adverse effect?" To establish causality, evidence should be consistent across populations, be of significant statistical strength, show specific outcomes linked to specific exposures, and provide coherence across various lines of evidence.[iv]	NTP explicitly does not employ a WoE assessment for the RoC program, but instead from an early stage in its process carries forward for further review only those positive data that may support a cancer concern. That this is true is proven by NTP's Draft Substance Profile (DSP) for styrene, which was the document peer reviewed by NTP's Board of Scientific Counselors at their February 2009 meeting on styrene. The styrene DSP made reference to only the positive data identified by NTP, despite a pointed effort by outside scientists to encourage NTP to also include a useful summary of the null and negative data.[v] Constrained in part by the RoC "listing criteria",[vi] NTP makes no effort to conduct the type of analysis recommended by NAS. A critical defect in the listing criteria is that NTP maintains that as long as *any one* of the criteria is met, there is no basis for not listing a substance as at least "reasonably anticipated" to be a carcinogen. This approach is unreasonably and unscientifically insensitive to the relative value of various studies. The listing criteria fail to distinguish between chemicals that are truly likely ("reasonably anticipated") to cause cancer, and those that have complex databases that *on the whole* fail to support a cancer concern. Another critical defect is that there is nothing in these criteria that suggests how new information is considered. Under the NTP criteria, once a single positive study in humans has been identified, it is not clear how at some point in time new or better information would supplant the previous study with the new information. This inability to modify the listing based on new or better science makes NTP's listing criteria inherently non-scientific.	NTP is making no effort to address the very serious shortcomings of the RoC listing criteria. Any effort to revise the RoC program that does not require full WoE assessment, consistent with the NAS roadmap, is negligent and fails to meet the legislative intentions associated with creation of the RoC . The proposed process would continue the improper practice of minimizing null and negative data. The proposed process specifies that both the concept document and the draft monograph are to contain summaries of "evidence <u>for</u> carcinogenicity" (emphasis added). Given all the criticism recently leveled at NTP for failing to consider negative and null data, especially in the case of styrene where the preponderance of the data fail to support a cancer concern, it is especially frustrating that NTP fails to make a good faith effort to identify and address this concern. The "concept document" to be prepared early in a substance's review will contain the "evidence <u>for</u> carcinogenicity". While in practice only the positive data were carried forward in the process, the Background Document prepared at this stage during the 12th RoC process was at least represented by the staff as including a complete review of studies. NTP is vague about the content of the draft Monographs. Especially since there is to be no comprehensive background document, the revised process must require that the draft Monograph contain a complete review and summary of all relevant studies, not just the limited positive data that support the staff's position.

Principle of scientific review to support hazard assessment	NTP's performance during the 12th RoC	NTP's new proposed RoC process
Peer review Peer review is widely accepted as a component of the scientific process necessary to ensure a reasonable standard of quality. Effective peer review helps ensure, first, that procedures, data, analyses and conclusions are presented in sufficient clarity and detail. Further, review by independent experts helps ensure that the procedures and analyses are consistent with accepted best practices and are appropriate for the specific study. Finally, peer review helps ensure that the conclusions drawn by the authors are reasonable. The Office of Management and Budget's Final Information Quality Bulletin for Peer Review emphasizes the value of timely review of scientific input: [I]n the context of risk assessments, it is valuable to have the choice of input data and the specification of the model reviewed by peers before the agency invests time and resources in implementing the model and interpreting the results. "Early" peer review occurs in time to focus attention on data inadequacies in time for corrections.[vii]	In preparing the 12th RoC, NTP specifically required that any information to be considered must come from peer reviewed sources.[viii] However, in three critical cases necessary to support its conclusion on styrene, NTP reinterpreted existing studies, arriving at conclusions contrary to those of the original authors and peer reviewers. In none of these cases did NTP prepare detailed descriptions of its reanalysis and submit them for peer review. This denies the scientific community and the public an opportunity to judge the soundness of NTP's reanalyses, and effectively hides the novel nature of these reanalyses from NTP's peer reviews. This kind of *reanalysis without peer review* can be used to support any presumptive conclusion, and is a blatant violation of good scientific process. For the 12th RoC, the NTP identified and selected members of the Expert Panels using a non-transparent and closed process, and for the styrene Panel at least two scientists had previously taken public positions that styrene should be considered a carcinogen. And if a Panel had the temerity to vote not to list a substance, as the glass wool Panel did, the staff disregarded the Panel's vote. NTP was obligated to use NTP's Board of Scientific Counselors, whose members are appointed by the Secretary. Yet the staff succeeded in minimizing the BSC's influence by presenting only very limited data, restricting the charge question to sufficiency of the staff's presentation rather than whether or not the overall database for a substance supports a cancer listing,[ix] provided only a brief opportunity for the BSC to evaluate the merits of public comment (and did not provide the BSC with any formal or timely response to public comment), and denying the BSC a formal "yes or no" vote on the Draft Substance Profile.	NTP's proposed process lessens even further the potential safeguards and quality control offered by peer review. Far too much of the peer review process is left to the staff's discretion on a case-by-case basis. According to its charter, the Board of Scientific Counselors is the group appointed by the Secretary to advise "on matters of scientific program content" and on the "scientific merit...and overall scientific quality" of the NTP. NTP cannot delegate this responsibility to an *ad hoc* group. The BSC must continue in its role as final reviewer of NTP's listing recommendations before they are sent to the Secretary. Further, the BSC must formally vote to approve or reject each monograph. Without a formal vote, NTP is free to characterize the opinions of the individual Board members any way they like. The only conceivable reason to deny a vote is to prevent the BSC from upsetting the staff after their considerable investment in preparing the draft monograph. This makes a mockery of what should be a very important peer review step, and again denies the Secretary the full value of the BSC review. Further, NTP must reform the process so that it may no longer improperly avoid formal peer review when the staff or panels create new science by reanalyzing published data. And finally, NTP must specifically engage the BSC in a review not just of the staff's position, but in a meaningful evaluation of analyses and conclusions submitted by outside scientists. This should include requiring the NTP to formally develop responses to public comments for evaluation of the adequacy of NTP positions by the BSC or other review mechanisms.

Principle of scientific review to support hazard assessment	NTP's performance during the 12th RoC	NTP's new proposed RoC process
Responding to outside scientific comment The practice of providing timely responses to relevant comments from the public, including outside scientists, is critical for several reasons. Carefully reviewing and preparing written responses to comments before starting the next step in a policy-setting process helps ensure that the agency has the benefit of data and analyses from a variety of sources early in the process, before the agency staff have committed to an unsubstantiated or malformed position. Further, the analysis of and responses to relevant outside comments, especially those that differ from the agency's position, are necessary for effective peer review. One of the most important objectives for good peer review is to provide the agency with a "reality check" of the validity of its analyses and conclusion compared to alternative analyses and conclusions. Peer reviewers can seldom be counted on to thoroughly review public comments and discover critical disagreements with the agency's position. Rather, a good faith effort at peer review requires the agency to provide reviewers with accurate and helpful summaries of outside comments. Since for the RoC, NTP's conclusion is actually a recommendation to the HHS Secretary, the Secretary's decision cannot fairly be said to be well informed unless NTP provides an accurate and helpful summary of any relevant outside scientific comments critical of NTP's position. In developing the Information Quality Bulletin for Peer Review, the Office of Management and Budget (OMB) emphasized: > In addition to selecting independent and qualified peer reviewers for regulatory science, it is also essential to grant the peer reviewers access to sufficient information and to provide them with an appropriately broad mandate. In the past some agencies have sought peer review of only narrow questions regarding a particular study or issue. While the scope of peer reviewers' responsibilities will necessarily vary by context, peer reviewers must generally be able to render a meaningful review of the work as a whole.[x] The accurate and transparent presentation of scientific information, including an explication of the underlying assumptions, contextualization of uncertainties, and explanation of the limitations of the body of scientific literature, is critical to informed decision making by the public and policymakers.[xi]	NTP's position on substances considered for listing in the 12th RoC were subject to review by three peer review panels, one comprised of NTP-selected scientists, an interagency panel, and the Board of Scientific Counselors. However, NTP directly provided these panels with summaries of only the positive data NTP believed supported its listing decision, while "making available" the extensive public comment only through posting on a website. NTP made no effort to provide the panels with summaries or other helpful information related to the extensive outside public comments explicitly disagreeing with the staff's position. NTP also failed to provide any timely rebuttal analyses to such disagreements to the review panels such that they could better judge the respective merits of the differing positions. At the NTP Board of Scientific Counselors meeting on styrene, members of the pubic were permitted to provide written and oral comments. However, the BSC's "key reviewers" for styrene had prepared extensive comments *before* being able to hear the public comments, and were anyway constrained by the staff's direction that they judge only the sufficiency of the presentation of information in the Draft Substance Profile, and whether given the staff's identification of positive studies the listing criteria had been satisfied. Again, a good faith effort at peer review would have required the staff to specifically engage the BSC in assessing the relative merits of the positions of the staff and of outside scientists. NTP claims that outside comments, and the 500-page NTP styrene Background Document, were posted on the RoC website and "made available" to peer reviewers. However, it was not realistic to expect panel members, without explicit direction from staff, to wade through well over 1,000 pages of scientific comment to find the key criticisms of the staff's position. The NTP offered a public response to comments only after the formal publication of the RoC. This belated timing did not allow any formal peer review of the adequacy of NTP's responses to external criticisms of its analyses, and implies that any formal disagreements with NTP's rebuttal must be relegated to a lengthy and cumbersome nomination process for subsequent RoCs.	The proposed process would delay even the receipt of public comment until well after NTP has already taken a position regarding the carcinogenicity of a substance. In the process employed for the 12th RoC, public comments were solicited on initial nomination of a substance, and in response to the draft and revised Background Documents. In the proposed revised process, NTP would not solicit comments until after preparation of the concept document which is to include "evidence for carcinogenicity". The proposed process fails to describe a *good faith* effort at really considering external scientific input, largely because it would continue the entirely inadequate process of "making available" public comments to peer reviewers by posting them on NTP's website. Panel review panel members are never likely to have the time or inclination to wade through what could easily be thousands of pages of public comment and identify the key data or analyses that may question the validity of NTP's position. Further, allowing the public to present information at peer review meetings does not advance the quality of peer review, unless the comments are presented before the peer reviewers begin preparing their own positions and the staff actively encourages the panel to fully consider the comments. A *good faith* effort at peer review would require NTP to prepare timely, accurate and helpful summaries of information submitted by outside scientists, including identification of critical disagreements with NTP's position, and then specifically require peer reviewers to consider the summary and public comments and determine the validity of NTP's position in light of the comments. Without *timely* summary and response to public comments, NTP's peer review practice again short circuits this very important quality control step, and denies the Secretary the full value of peer review.

Principle of scientific review to support hazard assessment	NTP's performance during the 12th RoC	NTP's new proposed RoC process
Conflict of interest Conflict of interest - both financial and intellectual - must be avoided during any peer review process. The National Academy of Science's Policy and Procedures on Committee Composition and Balance and Conflicts of Interest for Committees Used in the Development of Reports[xii] specifies the practices needed to minimize the contamination of peer review by the personal interests and biases of panel members.	NTP touts its conflict of interest policy as being rigorous, but its policy falls far short of the standard set by the National Academy of Sciences. Again, the styrene review provides particular insights into implementation issues associated with the current RoC process. In the case of the styrene Expert Panel, NTP selected a particular scientist to serve on the panel and chair its epidemiology subpanel, thereby placing this scientist in the uncomfortable position of having to review NTP's position on her own published work. During the Panel's review, the epidemiological subpanel, chaired by this panel scientist, re-analyzed a key epidemiology study (Delzell et al., 2006), reversed the published conclusions of the investigators of this peer-reviewed study, and developed new conclusions very similar to those reached by the panel scientist in her earlier and less comprehensive study of this same epidemiological cohort. What was of particular concern was that their change in interpretation of this key study served as the primary basis for the Panel (and subsequently the NTP) to show that the substance met the human carcinogenicity criterion in the proposed NTP listing. The National Academy of Sciences' policy on conflict of interest would not have prohibited the particular scientist in question from serving on the panel. However, the policy would have made her review of her own work and the work of other scientists on the same cohort an issue that the NTP would have had to deal with transparently. In addition, the public would have had an opportunity to weigh in on the issue before the panel met. NTP staff also placed on the styrene Expert Panel a scientist from a state regulatory agency who had long advocated within her own agency to characterize styrene as a carcinogen "as a matter of policy" (independent of the science). This certainly suggests that NTP was not really interested in an objective and unbiased look at the styrene science.	NTP makes no effort to improve its recognition and management of potential conflict of interest and bias. With so much of the process left up to the staff to determine on a substance-by-substance basis, it will be even more likely that assessments are intellectually tainted.

[i] Chapter 7 of the NAS *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde*. April, 2011. http://www.nap.edu/catalog.php?record_id=13142. While this Chapter is included in the NAS's review of the EPA formaldehyde assessment, the practices recommended by the NAS in this chapter have broad applicability to all hazard assessments, including those of the *RoC*.

[ii] *Improving the Use of Science in Regulatory Policy*, pp. 41-42, Bipartisan Policy Center (Aug. 5, 2009).

[iii] Two real world examples of refinement of the weight-of-the-evidence approach, one cited by NAS and one published subsequently are: Improving the Presumptive Disability Decision-Making Process for Veterans (2008, Institute of Medicine), cited by NAS on page 117 of its Report; and Endocrine Disruptor Screening Program: Weight-of-Evidence: Evaluating Results of EDSP Tier 1 Screening to Identify the Need for Tier 2 Testing (September 14, 2011, EPA).

[iv] See Table 7-1 of the NAS document at Note i.

[v] Indeed, hiding null and negative data from reviewers appears to be NTP's policy. At the June 21, 2010 meeting of the Board of Scientific Counselors called to review several draft profiles prepared for the Report on Carcinogens, Dr. Gloria Jahnke of NTP presented and explained the NTP draft profile on glass wool fibers. Following her presentation, Dr. Nagorkatti, a member of the BSC panel, asked Dr. Jahnke: "I'm just wondering whether there were not studies on other animals such as mice, or they were done and found not to be carcinogenic." Dr. Jahnke replied: "The inhalation study of monkeys was negative. So, I'm not recording negative data here; I am recording data that supports our call. So that's why you didn't see it." Emphasis added. This exchange can be found at 12:30 minutes on the recording at www.box.net/shared/static/sxqzg12pkr.mp3.

[vi] NTP Listing Criteria: http://ntp.niehs.nih.gov/go/15209.

[vii] "Final Information Quality Bulletin for Peer Review," Memorandum from Joshua B. Bolten, Director, Office of Management and Budget, Executive Office of the President to Heads of Departments and Agencies, p. 14 (Dec. 16, 2004).

[viii] "Data used to prepare [the RoC] must come from publicly available, peer-reviewed sources." NTP Report on Carcinogens Review Process, at http://ntp.niehs.nih.gov/go/29353. In a letter to Congressman Rick Boucher on September 30, 2009, NTP Director Linda Birnbaum wrote, "Per NTP guidelines, the human cancer, experimental animal, and mechanistic scientific information included in the background document and considered in the evaluation of styrene must come from publicly available peer-reviewed sources." And again, "Per NTP policy, the scientific evidence cited in support of the NTP's policy decision must come from publicly available, peer-reviewed sources." Note that Dr. Birnbaum does not limit her statements to a narrow definition of "data."

[ix] The NTP charge to the BSC was "The BSC is charged to determine whether the scientific information cited in the draft substance profile for a candidate substance is technically correct, clearly stated and supports the NTP 's policy decision regarding its listing in the RoC. *The BSC is <u>not</u> asked to review the NTP 's decision regarding listing status*" (emphasis added). *NTP Report on Carcinogens Review Process*, at http://ntp.niehs.nih.gov/go/29353.

[x] *OMB Proposes Draft Peer Review Standards for Regulatory Science*, Office of Management and Budget, Executive Office of the President, p. 4 (Aug. 29, 2003).

[xi] See "Memorandum on Scientific Integrity," From John P. Holdren, Assistant to the President for Science and Technology and Director of the Office of Science and Technology, to the Heads of the Executive Departments and Agencies, p. 2 (Dec. 17, 2010).

[xii] http://www.nationalacademies.org/coi/index.html